

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

CYPERMETHRIN

Chemical Code # 2171, Tolerance # 418
SB 950 # 337

November 3, 1994
Revised June 21, 2001 and February 6, 2002

I DATA GAP STATUS

Chronic toxicity, rat:	no data gap, no adverse effect
Chronic toxicity, dog:	no data gap, no adverse effect
Oncogenicity, rat:	no data gap, no adverse effect
Oncogenicity, mouse:	no data gap, possible adverse effect
Reproduction, rat:	no data gap, possible adverse effect
Teratology, rat:	no data gap, no adverse effect
Teratology, rabbit:	no data gap, no adverse effect
Gene mutation:	no data gap, no adverse effect
Chromosome effects:	no data gap, no adverse effect
DNA damage:	no data gap, no adverse effect
Neurotoxicity:	not required at this time, possible adverse effect indicated

Toxicology one-liners are attached.

All record numbers through 184009 and 984941 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T010621

Prepared by Stanton Morris, 6/21/01; revised by Gee, 2/06/02

Note: There are two subchronic studies in the dog which are not on file as of 2/6/02 and should be submitted before risk assessment. (Gee, 2/5/02).

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

**418-041; 037987; "Cypermethrin: 2 Year Feeding Study in Rats", Report No: CTL/P/669; G.M. Milburn, D. Forbes, P.B. Banham, I.S. Chart, M.J. Godley, C.W. Gore, I. Pratt, M.D.C. Scales, M.D. Stonard, and B.H. Woollen; Imperial Chemical Industries PLC, UK; 6/28/82. Groups of 64 or 128 (0 ppm) Wistar rats/sex were given cypermethrin (batches P19, P24, P26; 88.2 to 93.1% stated purities) in the diet at 0, 20, 150, or 1500 ppm for 104 weeks. At 52 weeks 12 or 24 (0 ppm) rats/sex/group were sacrificed. The high dose was initially 1000 ppm but was raised to 1500 ppm between weeks 3 and 6. Effects seen in both sexes at 1500 ppm were: decreased incidence of distended abdomen, body weight gain, food consumption, red cell volume, plasma cholesterol, plasma triglycerides, urine volumes, and liver, kidney, spleen and heart weights; and increased incidence of hair loss, lymphocyte count, plasma urea, and liver aminopyrine N-demethylase activity and smooth endoplasmic reticulum (NOEL = 150 ppm). No adverse effect was indicated. The study was unacceptable (J. Christopher, 8/27/85; S. Morris and J. Gee, 3/17/94) but upgraded by evaluation of the collective data (H. Greene and S. Morris, 1/12/1).

418-191; 146312: This document contains an incomplete copy of a 90-day feeding study ("PP383: 90 Day Feeding Study in Rats," Report No. CTL/P/327; J.R. Glaister et al., Imperial Chemical Industries Limited, Cheshire, UK; 1/8/80; DPR doc. # 418-191, rec. # 146312), inter group comparisons of clinical observations, and certificates of analysis for batches P19, P24 and P26. The 2-year study is upgraded to acceptable based on a review of the collective data, especially body weights in the 90-day study (S. Morris and J. Gee, DPR Response, 1/12/1).

418-042; 037988: This document contains individual data for the study at DPR doc. # 418-041, rec. # 037987.

418-011; 981937: This document contains a partial duplicate of the study at DPR doc. # 418-041, rec. # 037987.

418-012; 984939: This document contains preliminary data for the study at DPR doc. # 418-041, rec. # 037987.

418-016; 005809: This document contains preliminary data for the study at DPR doc. # 418-041, rec. # 037987.

418-017; 003024: This document contains preliminary data for the study at DPR doc. # 418-041, rec. # 037987.

CHRONIC TOXICITY, RAT

See COMBINED, RAT above.

418-040; 037986; "Toxicity Studies on the Insecticide WL 43467: A Two Year Feeding Study in Rats", TLGR.0189.78; H.E. McAusland, S.T.G. Butterworth, and P.F. Hunt; Shell Toxicology Laboratory (Tunstall); 2-79. Groups of 48 (treated) or 96 (controls) Wistar rats/sex were given dietary mixtures of Cypermethrin (WL 43467, batch 30, 98% stated purity) at 0, 1, 10, 100, or 1000 ppm. Six or 12 (controls) rats/sex/group were sacrificed at 6 and 12 months, 12 or 24 (controls) at 18 months and the remaining 24 or 48 (controls) at 24 months. The only treatment-related effect was decreased group mean body weight and food consumption relative to controls of both sexes at 1000 ppm (NOAEL > 1000 ppm). No adverse effect was indicated. The study was unacceptable and not upgradeable because of inadequate analytical method and data, no rationale for the doses used, inadequate serum chemistry data, no urinalysis or ophthalmological performed, and not all individual data (S. Morris and J. Gee, 1/28/94).

CHRONIC TOXICITY, DOG

** 418-190; 143500, "A Chronic (12-Month) Oral Toxicity Study of FMC 30980 Technical in the Dog via Dietary Administration," Study No. # 92-3115, FMC No. A93-3821; I. W. Daly; Pharmaco LSR, Inc., East Millstone, New Jersey; 11/7/95. Groups of 4 Beagle dogs per sex were fed dietary mixtures of cypermethrin (technical, FMC 30980, 95.7% purity) at 0, 100, 200, 600, or 1100 ppm for 12 months. Treatment related effects included death or sacrifice of moribund males at 600 ppm (1/4) and 1100 ppm (2/4), tremors and irregular gait in males at 600 ppm (2/4) and in both sexes at 1100 ppm (8/8) and decreased body weight gain in both sexes at 600 and 1100 ppm (NOEL = 200 ppm). No adverse affect was indicated. The study was acceptable (H. Green and S. Morris, 5/15/1).

418-070; 069574; "Cypermethrin: One Year Oral Dosing Study in Dogs", Report No: CTL/P/703; A.E. Kalinowski, P.B. Banham, I.S. Chart, S.K. Cook, C.W. Gore, and S.F. Moreland; Imperial Chemical Industries PLC, Central Toxicology Laboratory, UK; 7/6/82. Cypermethrin (batch P26, 90.6% stated purity, corn oil vehicle) was given daily in gelatin capsules to 6 beagle dogs/sex/group for 52 weeks at 0, 1, 5, or 15 mg/kg/day. Effects seen at 15 mg/kg/day in both sexes were: transient neurological effects (whole body tremors, gait abnormalities, incoordination, excitability, disorientation, and hypersensitivity to noise), vomiting the first week of treatment, and decreased growth rates. A treatment related increase in liquid feces was seen at 5 and 15 mg/kg/day (NOEL = 1 mg/kg/day). No adverse effect was indicated. The study was unacceptable but possibly upgradeable with adequate submissions of analysis of the test material, individual clinical and ophthalmology data, and an adequate rationale for the doses used (S. Morris and J. Gee, 3/2/94).

418-013; 984940: This document contains a partial duplicate of the study at DPR doc. # 418-070, rec. # 069574.

418-192; 146313; "Cypermethrin: 6-Week Oral Dosing Study in Dogs," Report No: CTL/P/490, A.E. Kalinowski et al.; Imperial Chemical Industries Limited, Cheshire, UK; 8/18/80. Groups comprised of one male and one female beagle dogs were given single daily oral doses of cypermethrin (PP383, 91.5%, reference P19, corn oil vehicle) in gelatin capsules at 0, 10, 25, and 50 mg/kg/day for 6 weeks. Treatment-related neurological effects were seen in all dogs at 25 and 50 mg/kg/day that included lack of coordination and muscle tremors. One 50 mg/kg/day male was sacrificed after two episodes of convulsions. Other treatment-related effect seen at 25 and 50 mg/kg/day included gastro-intestinal disturbances, reduced body weight gain, temporary decreases in food intake. Hepatic fatty changes of the smooth endoplasmic reticulum and altered plasma enzyme profiles were seen in the surviving male at 50 mg/kg/day. All treatment groups had increased levels of aminopyrine N-demethylase activity and the 25 mg/kg/day group showed proliferation of smooth endoplasmic reticulum that was indicative of enzyme induction. The data are not adequate to justify the doses used in the main study (Morris, 1/12/1).

418 - 079 184009 "Review and discussion of cypermethrin chronic dog studies." (FMC Corporation, 6/8/2000) The three-page document discussed the two one-year dog studies (records 069574 and 143500) and the comparison of the NOELs. The position of FMC was that the more recent dietary study (143500) should be used by US EPA for regulatory purposes rather than the earlier study with dosing via gelatin capsules. The NOEL with capsules was 1 mg/kg based on gastrointestinal disturbances (ex.: watery stools without microscopic pathology) versus 200 ppm (5.7 mg/kg/day for males, 6 mg/kg/day for females) when fed in the diet. The NOEL for clinical signs of neurotoxicity was 5 mg/kg with capsules and 200 ppm with the diet being similar in the two studies. The discussion also cites two subchronic studies that were not found on file with the Department. No worksheet. (Gee, 2/5/02).

The citations for these two studies were:

"Toxicology studies on the pyrethroid insecticide WL 43467 [cypermethrin]: a 13-week feeding study in dogs." (FMC No. A80-461, November, 1977) The NOEL was given as 500 ppm based on a LOEL of 1500 ppm for clinical signs of neurotoxicity. *This study should be submitted.*

"A subchronic (3-month) oral toxicity study of FMC 30980 technical in the dog via dietary administration." (Daly, I. W., Study No. 92-3114, FMC No. A92-3706, March 31, 1994) The doses in this study were 0, 300, 600, 800 and 1100 ppm with a NOEL of 600 ppm (20 mg/kg/day) based on clinical signs and reduced body weights and food consumption. *This study should be submitted.*

ONCOGENICITY, RAT

See COMBINED, RAT above.

ONCOGENICITY, MOUSE

****418-043; 037989;** "Cypermethrin: Lifetime Feeding Study in Mice", Report No: CTL/P/687; S. Lindsay, P.B. Banham, I.S. Chart, D.T. Chalmers, M.J. Godley, and K. Taylor; Imperial Chemical Industries, Central Toxicology Laboratory, UK; 6/23/82. Groups of 60 or 120 (0 ppm) Swiss mice/sex were fed for up to 101 weeks diets containing cypermethrin (3 batches; 91.5, 94.2, 94.0% stated purity) at 0, 100, 400, or 1600 ppm. Ten or 20 (0 ppm) mice/sex/group were sacrificed at 52 weeks. Treatment-related effects at 1600 ppm were decreased body weight gains of both sexes in the first 12 weeks and increased terminal liver weights, decreased interim testes weights, and changes in the distribution of formed blood elements of males (non-oncogenic NOEL = 400 ppm). A possible adverse effect was indicated by an increased incidence in benign alveologenic tumors in females at 1600 ppm. The study was unacceptable(J. Christopher 8/27/85; S. Morris and J. Gee, 3/9/94) but upgraded by adequate submissions of analytical data and rationale for the doses used (Morris & Gee, Rebuttal, 6/21/01).

418-044; 037990: This document contains individual data for the study at DPR doc. # 418-043, rec. # 037989.

418-011; 984938: This document contains a partial duplicate of the study at DPR doc. # 418-043, rec. # 037989.

418-191; 146312: This document contains the certificate of analysis for batch P19 but not batches ACD/79/134 and 47.

418-193; 146314; "Cypermethrin: 28-day Feeding Study in Mice, CTL/P/534," A. Moyes et al., Imperial Chemical Industries Limited, Cheshire, UK; 8/25/81. Groups of 16 mice/sex/dose were feed dietary mixtures of cypermethrin (batch P19, 91.5% stated purity) at 0, 100, 400 or 1200 ppm for 28 days or 40 ppm for 14 days followed by 4500 ppm for 14 days. Treatment-related effects included decreased body weight gain in both sexes and increased liver weights in males at 40/4500 ppm and, at 1200 ppm, increased hepatic aminopyrine demethylase activity and smooth endoplasmic reticulum in both sexes and increased liver weight in females. The study "concluded that a top dose level of at least 1200 ppm cypermethrin could be used on a long term study" (p. 1). A satellite study fed groups of 4 mice/sex/dose dietary mixtures of the test material at 2000, 4000, 6000 or 8000 ppm for 14 days. The group mortality rates were 3 / 4 for males and 2 / 4 for females at 6000 and 8000 ppm. There were no mortalities at 2000 and 4000 ppm. Ataxia was seen at 6000 and 8000 ppm. Pilo erection, ungroomed and hypersensitivity to touch and noises were seen at 2000 and 4000 ppm. The study concluded that "a dose level of 4000 ppm is unlikely to produce many observable clinical symptoms" (p. 54). (S. Morris and J. Gee, 1/25/1).

REPRODUCTION, RAT

****418-045; 037991;** "Cypermethrin: Three Generation Reproduction Study in the Rat", Report No: CTL/P/683; G.M. Milburn, P.B. Banham, R.D.N. Birtley, M.J. Godley, and S.F. Moreland; ICI Central Toxicology Laboratory, Alderley Park, UK; 7/9/82. Groups of 15 male and 30

female Wistar rats were continuously exposed to diets containing cypermethrin (batches P19, P24, P26; 91.5, 93.1, 90.6% stated purity) at 0, 50, 150, or 750 ppm for 3 generations (F0, F1, F2) with 2 litters/generation (F1a, F1b, F2a, F2b, F3a, F3b). The high dose F0's received 1000 ppm for the first 12 weeks and 750 ppm thereafter. The F0's were first bred at 12 weeks. Ten days after weaning the F1a pups the F0's were bred again to produce the F1b pups. Selected F1b weanlings were exposed for 11 weeks then bred similarly to the F0's to produce the F2a and F2b litters. This cycle was repeated with selected F2b weanlings to produce the F3a and F3b litters. The initial high dose of 1000 ppm produced transient neurological effects between days 3 and 22 in the majority of both sexes of the F0 parents and the death of one male on day 9. Decreased adult body weight gain was seen in F0's in both sexes at 1000 ppm and females at 150 ppm; in F1 females at 750 ppm; and both F2 sexes at 150 and 750 ppm. Adult food consumption was reduced for both F0 sexes at 1000 ppm and F0 females at 150 ppm; and both F1 and F2 sexes at 750 ppm (parental NOEL = 50 ppm). There were no treatment-related effects on reproductive parameters. A **possible adverse effect** was indicated by group mean pup weight gains in the 750 ppm group that were less than controls: for both sexes in all litters at 21, and 28 days post partum and for both sexes in the F1A, F1B, F2B, and F3B litters at 10 days post partum and in pilot studies decreased live litter size and pup survival at 750 and 1000 ppm and, decreased birth weights and body weight gain at 1000 ppm and in weaned pups, increased incidences of ataxia, gait abnormalities and hypersensitivity to noise and decreased pup body weight in both sexes at 1000 ppm (developmental NOEL = 150 ppm). The study was unacceptable (S. Morris and J. Gee, 3/1/94) but upgraded by with adequate submissions of analytical data for the test material, a rationale for the high dose, compiled gross and histopathology observations, compiled male reproductive and mating performance data, and individual and compiled clinical data for all animals for the entire study (S. Morris and J. Gee, 6/21/1).

418-046; 037992: This document contains individual data for the study at DPR doc. # 418-045, rec. # 037991.

418-013; 984941: This document contains a partial duplicate of the study at DPR doc. # 418-045, rec. # 037991.

418-194; 146315: This document contains two preliminary studies ("Cypermethrin: Preliminary Reproduction Study to Determine the Maximum Tolerated Dose of Cypermethrin in Weanling Rats," Report Number: CTL/P/565, 1981 and "Cypermethrin: Preliminary Study in the Rat to Determine Dose Levels for a Three-generation Reproduction Study," Report Number: CTL/P/501, 7/31/80) and adequate submissions of analytical data for the test material, a rationale for the high dose, compiled gross and histopathology observations, compiled male reproductive and mating performance data, and individual and compiled clinical data for all animals for the entire study (Morris 2/26/1).

418-195; 146316: This document contains a signed GLP statement for the study at DPR doc. # 418-045, rec. # 037991.

418-040; 037985; "Toxicity Studies on the Insecticide WL 43467: A Three Generation Reproduction Study in Rats", TLGR.0188.78; R.W. Hend, R. Hendy and D.J. Flemming; Shell Toxicology Laboratory (Tunstall); 2-79. Groups of 30 Wistar rats/sex were continuously

exposed for three generations (F0, F1, F2) with 2 litters/generation to dietary concentrations of cypermethrin (WL 43467, batch 30, 98% stated purity) at 0, 10, 100, or 500 ppm. F0 adults were exposed for 5 weeks before breeding, through two breeding, gestation, and weaning cycles to produce the F1a and F1b litters. F1b pups were exposed for at least 10 weeks then through two breeding, gestation, and weaning cycles to produce the F2a and F2b litters. F2b pups were treated similar to the F1b's to produce the F3a and F3b litters. Post-weaning bodyweight gain and food consumption were reduced at 500 ppm in both sexes and all generations except for the F2 male bodyweight gain and F1 and F2 male food consumption (NOEL = 100 ppm). There were no other treatment-related effects on parental animals, reproductive performance, or pups. No adverse effect was indicated. The study was unacceptable and not upgradeable because there were no analytical data for the test material, no description of the technique used for the diet analysis, no rationale the doses used, inadequate necropsy and histopathology data, and no individual parental data (S. Morris and J. Gee, 1/21/94).

TERATOLOGY, RAT

**418-040; 037982; "WL 43467: Effects Upon the Progress and Outcome of Pregnancy in the Rat", LSR Report No. 78/SHL2/364; J.M. Tesh, S.A. Tesh, and W. Davies; Life Science Research, Stock, Essex, England; 10/4/78. Cypermethrin (WL 43467, batch no. 30, 98.2% stated purity, corn oil vehicle) was given by oral gavage to groups of 25 pregnant female Sprague-Dawley CD rats at 0, 17.5, 35, or 70 mg/kg/day on gestation days 6 through 15. The animals were sacrificed on gestation day 21 and the maternal reproductive organs were examined. The fetuses were weighed and examined for external, skeletal, and visceral abnormalities. Maternal effects were seen at 70 mg/kg/day: transient post-dosing neurological disturbances (11/25); convulsions (1/25); and death (2/25). Bodyweight gain was decreased at 35 and 70 mg/kg/day (maternal NOEL = 17.5 mg/kg/day). There were no treatment related developmental effects (developmental NOEL = 70 mg/kg/day). No adverse effect was indicated. The study was unacceptable (S. Morris and J. Gee, 1/14/94) but graded with adequate submissions of analyses of WL 43467 (batch no. 30) and the dosing solutions (S. Morris and J. Gee, 6/21/01).

418-001; 035023:

418-001; 984934:

418-005; 984934: This document contains a brief summary of the study at DPR doc. # 418-040, rec. # 037982 (J. Christopher, 8/27/85).

418-058; 064620: This document contains a brief statement about the study at DPR doc. # 418-040, rec. # 037982.

418-195; 146316: This document contains statements about the study at DPR doc. # 418-040, rec. # 037982. Evaluation of these data upgraded the main study to acceptable (S. Morris, 6/21/01).

TERATOLOGY, RABBIT

** 418-166; 133309; "Cypermethrin Technical Oral Teratology Study in Rabbits," Study Number # A93-3822; C. Freeman, FMC Corporation Toxicology Laboratory, Princeton, NJ.; 10/28/94. Groups of 20 mated female New Zealand White rabbits were given single oral doses of cypermethrin (technical, 95.7% purity, reference # PL91-333, 0.2 to 1.4 ml of 50% solution, corn oil vehicle) by oral gavage at 0 (1.4 ml), 100 (0.2 ml), 450 (0.9 ml), or 700 (1.4 ml) mg/kg/day on gestation days 7 through 19. Pups were delivered by Cesarean section and does sacrificed on gestation day 29. Uteri were examined for implantation sites, resorptions and dead and live fetuses. Ovaries were examined for corpora lutea. Fetuses were counted, weighed, externally examined, dissected, and internally sexed. Following microscopic internal examination of soft tissues, fetuses were cleared in 1% potassium hydroxide for skeletal examination. One 100 mg/kg/day and one control animal died/sacrificed due to misdosing. One 700 mg/kg/day animal was sacrificed in extremis due to swelling, scabbing, and severe ulceration of the vaginal area. One 450 mg/kg/day animal was terminated after aborting on day 26. Treatment-related maternal effects included pink or red staining of the cage pan liner at 450 and 700 mg/kg/day and abdominogenital staining, anorexia, decreased feces, ataxia, and swelling, scabbing, and severe ulceration of the vaginal area (maternal NOEL = 100 mg/kg/day). There were no treatment-related effects on litter parameters, fetal development or incidence of fetal malformations or skeletal anomalies (fetal NOEL \$ 700 mg/kg/day). No adverse teratology effect was indicated. The study was acceptable.(H. Green and S. Morris, 1/8/1).

418-196; 146317: Exact duplicate of DPR doc. # 418-166, rec. #133309.

418-165; 133011; Dosing levels in DPR doc. # 418-166, rec. #133309 were based on "Cypermethrin Technical Pilot Oral Teratology Study in Rabbits," Study Number A93-3823; Christine Freeman, FMC Corporation Toxicology Laboratory, Princeton, New Jersey; October 14, 1994. Groups of 8 mated female New Zealand White rabbits were given single oral gavages of cypermethrin (technical, 93.4% purity, reference # PL91-333, 0.2 to 2.0 ml of 50% solution, corn oil vehicle) at 0 (2.0 ml), 100 (0.2 ml), 500 (1.0 ml), 750 (1.5 ml), or 1000 (2.0 ml) mg/kg/day on gestation days 7 through 19. Pups were delivered by Cesarean section and does sacrificed on gestation day 29. Uteri were examined for implantation sites, resorptions and dead and live fetuses. Ovaries were examined for corpora lutea. Fetuses were counted, weighed, externally examined, and internally sexed. One 1000 mg/kg/day and one control animal died/sacrificed due to misdosing. Treatment-related maternal clinical signs seen at 750 and 1000 mg/kg/day included abdominal spasms, anorexia, decreased feces, diarrhea, ataxia, pink or reddish-brown staining of cage pan liner, nasal discharge, and unthriftiness. One dam aborted at 750 mg/kg/day and 3 at 1000 mg/kg/day (maternal NOEL = 500 mg/kg/day). There were no other treatment-related effects on uterine, reproductive, fetal parameters or fetal external malformations (fetal NOEL \$ 1000 mg/kg/day). No adverse teratology effect was indicated. No worksheet was done (H. Green, and S. Morris, 1/8/1).

418-040; 037983; "Toxicity of WL 43467: Teratological Studies in Rabbits Given WL 43467 Orally", Group Research Report TLGR.0010.78; K.M. Dix; Shell Toxicology Laboratory (Tunstall); January, 1978. Cypermethrin (WL 43467, batch no. 30, 98.2% stated purity, corn oil

vehicle) was given orally in gelatin capsules to groups of 20 pregnant female banded Dutch rabbits at 0, 3, 10, or 30 mg/kg/day on gestation days 6 through 18. The animals were sacrificed on gestation day 28 and the maternal viscera and reproductive organs were examined. The fetuses were weighed and examined for external, skeletal, and visceral abnormalities. No treatment-related maternal or developmental effect was seen at any dose (maternal and developmental NOEL's > 30 mg/kg/day. No adverse effect was indicated. The study was unacceptable but possibly upgradeable with submission of adequate analytical data and rationale for the doses used (S. Morris and J. Gee, 1/18/94).

418-001; 035022:

418-001; 984934:

418-005; 984934: This document contains a brief summary of the study at DPR doc. # 418-040, rec. # 037983 (J. Christopher, 8/27/85).

GENE MUTATION

** 418-157; 124247; "Salmonella/Mammalian-Microsome Mutagenesis Assay", T1713.501; S. Haworth; Microbiological Associates, Bethesda, MD; 4/2/82. Cypermethrin (FMC 45806, test material identity and purity not stated, DMSO solvent) was tested in a bacterial reverse mutation assay using histidine auxotrophic strains of *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA100, and TA98). One trial was conducted with 3 plates/strain/dose being exposed for 48 hours to 0, 100, 500, 2500, 5000, or 10,000 : g/plate with or without metabolic activation (S9 fraction of Aroclor 1254-induced, male Sprague-Dawley rat liver homogenates). The plates were scored for colonies of prototrophic revertants. There was no treatment-related effect on reverse mutation rate. No adverse effect was indicated. The study was unacceptable (S. Morris and J. Gee, 3/22/94) but upgraded by submission of adequate identification and statement of purity for the test material (S. Morris and J. Gee, 4/18/01).

418-197; 146318: This document contained adequate identification and statement of purity for the test material (lot B81-36, 94.7%) for DPR doc. # 418-157, rec. # 124247 (S. Morris, 4/18/01).

418-022; 001841; "An Examination of Cypermethrin for Potential Mutagenicity using the Salmonella/Microsome Reverse Mutation Assay", CTL/P/595; R.W. Trueman; Imperial Chemical Industries Limited, Central Toxicology Laboratory, UK; 11/13/80. Cypermethrin (batch P19, 91.5% stated purity) was tested in a bacterial reverse mutation assay using histidine auxotrophic strains of *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA100, and TA98). Two trials were conducted with 3 plates/strain/dose being exposed for 72 hours to 0, 4, 20, 100, 500, or 2,500 : g/plate with or without metabolic activation (S9 fraction of Aroclor 1254-induced, Sprague-Dawley rat liver homogenates). The plates were scored for colonies of prototrophic revertants. There was no treatment-related effect on mutation rate. No adverse effect was indicated. The study was unacceptable and not upgradeable because there were no positive controls without activation and no rationale for the doses used (J. Christopher, 8/27/85; one-liner, S. Morris, 3/24/94).

418-022; 001842; "Toxicity Studies with Agricultural Chemicals: Mutagenicity Studies with Ripcord in Microorganisms In Vitro and in the Host-Mediated Assay", TLGR.80.059; T.M. Brooks; Shell Toxicology Laboratory (Tunstall); 6/80. Cypermethrin (WL43467, >98% stated purity, DMSO vehicle) was tested in microbial mutation assays using histidine auxotrophic strains of Escherichia coli (WP2, WP2 uvrA) and Salmonella typhimurium (TA1535, TA1537, TA1538, TA100, and TA98). In 2 trials, E. coli or S. typhimurium were plated with the test material at 0, 0.2, 2.0, 20, 200, or 2000 ug/plate with (2 or 3 plates/dose) or without (4 or 5 plates/dose) S9 metabolic activation and 48 hours later scored for prototrophic colonies. No adverse effect was indicated. The study was unacceptable and not upgradeable because of inadequate analytical data, no positive control without S9, metabolic activation system was not described, and inadequate protocol description (J. Christopher, 8/27/85; one-liner, S. Morris, 3/24/94).

CHROMOSOME EFFECTS

**418-022; 001840; "Toxicity studies with WL 43467: Chromosome studies on bone marrow cells of Chinese hamsters after two daily oral doses of WL 43467", TLGR.0136.77; B.J. Dean; Shell Toxicology Laboratory (Tunstall); 12/77. Groups of 6 Chinese hamsters/sex were dosed by oral gavage with cypermethrin (WL 43467, purity not stated, DMSO vehicle) at 20 or 40 mg/kg/day for 2 days. The animals were treated with Colcemid (0.04% solution, 0.01 ml/g b.w., i.p.) 90 minutes before being killed 8 or 24 days after the last dose and chromosome spreads were prepared from femoral bone marrow. One hundred metaphase cells from each animal were examined for chromosome aberrations. There was no treatment-related effect on chromosome aberrations. No adverse effect was indicated. The study was unacceptable but possibly upgraded with adequate submissions of analysis of the test material and dosing solutions and an adequate rationale for the doses used (J. Christopher, 8/27/85; one-liner, S. Morris, 3/24/94; S. Morris, 6/21/01).

418-198; 148545: This document contains an adequate rationale for analysis of the test material and doses used in the study at DPR doc. #418-022, rec. #001840. See work sheet (S. Morris, 6/21/01).

DNA DAMAGE

**418-186; 142302; "In Vivo-In Vitro Rat Hepatocyte Unscheduled DNA Synthesis Assay", Report # G95AQ06.381007; R.H.C. San and J.E. Sly; Microbiological Associates, Inc., Rockville, MD; 10/13/95. Groups of 10 male Fisher 344 rats were give single doses of Cypermethrin (technical, Lot # PL91-333, 95.4% purity, neat) by oral gavage at 0 (distilled water), 1.25, 2.5, or 5.0 g/kg. Groups of 3 rats/dose were sacrificed 1 to 3 or 12 to 16 hours after dosing. The animal's livers were harvested and primary hepatocyte cultures were prepared by partial digestion with collagenase. Hepatocyte viability was assessed by trypan blue exclusion. At least 6 cultures / rat containing approximately 5×10^5 cells were plated. Ninety to 180 minutes after plating, the cells were washed, incubated for 4 hours in medium containing 10 FCI ^3H -TdR/ml, washed 3 times, incubated in ^3H -free medium for 17 to 20 hours, washed, nuclei

swelled, cells fixed, developed 5 to 12 days with autoradiographic emulsion and stained. Silver grains were microscopically counted for equal areas of nuclei and cytoplasm from 50 cells / 3 replicates / rat / dose / time point. The positive and negative controls were adequate. There were no treatment-related effects on net (nuclear – cytoplasmic) grain counts. No adverse effect was indicated. The study was acceptable (H. Green and S. Morris, 5/19/01).

418-098; 091345; "Cypermethrin: Assessment for the Induction of Unscheduled DNA Synthesis in Rat Hepatocytes", Report No: CTL/P/3080; J.C. Kennelly; ICI Central Toxicology Laboratory, Cheshire, UK; 8/20/90. Cypermethrin (technical, batch number P32, 74.8% stated purity, corn oil vehicle) was given to male Alderley Park rats by oral gavage at 0, 100, or 200 mg/kg. Four or 12 hours later, hepatocytes were isolated and cultured in the presence of 3H-thymidine for 4 hours. Unscheduled DNA synthesis (UDS) was determined by autoradiographic analysis of tritium incorporation into nuclear material. Two trials were run with a total of 5 treated rats/dose/time point. The positive controls were adequate. There was no treatment-related increase in UDS. No adverse effect was indicated. The study was unacceptable and not upgradeable because there were no analysis of the dosing materials, no hepatocyte viability data, and the assay could not detect rapidly-repaired DNA damage (S. Morris and J. Gee, 2/4/94).

418-022; 035025; "Toxicity Studies with Agricultural Chemicals: Mutagenicity Studies with Ripcord in Microorganisms In Vitro and in the Host-Mediated Assay", TLGR.80.059; T.M. Brooks; Shell Toxicology Laboratory (Tunstall); 6/80. Cypermethrin (WL 43467, >98% stated purity, DMSO vehicle) was tested in microbial gene conversion assay using a histidine/tryptophan auxotrophic strain of *Saccharomyces cerevisiae* (JD1). In 2 trials, samples of liquid suspension cultures of *S. cerevisiae* were exposed at 0, 0.01, 0.1, 0.5, 1.0, or 5.0 mg/ml for 1 or 4 hours with or 1 hour without S9 metabolic activation. The samples were plated on selection media with 4 plates/dose/time point/loci and 3 days later scored for histidine or tryptophan prototrophic colonies. In 3 trials, 3 mice/dose were dosed by oral gavage with 0, 25, or 50 mg/kg. Immediately after dosing, suspensions of *S. cerevisiae* were injected ip into each mouse. Five hours later suspensions of *S. cerevisiae* were harvested and plated on selection media with 4 plates/dose/loci and 3 days later scored for histidine or tryptophan prototrophic colonies. No adverse effect was indicated. The study was unacceptable and not upgradeable because of inadequate analytical data, DMSO vehicle, metabolic activation system was not described, insensitivity of the host mediated assay, and inadequate protocol description (J. Christopher, 8/27/85; one-liner, S. Morris, 3/24/94).

418-186; 142303: This document contains analytical data on stability for cypermethrin technical, PL91-333 (S. Morris, 5/19/01).

NEUROTOXICITY

418-001; 035024: This document contains a summary of a study in which 10 male rats/dose were fed diets containing 0, 1250, 2500, or 5000 ppm of cypermethrin for 14 days. Clinical signs of neurotoxicity were seen at 1250, 2500, and 5000 ppm. A possible adverse effect was indicated by histopathological damage of the sciatic nerve seen in one 5000 ppm animal. The

study was unacceptable because it was only a summary (J. Christopher, 8/27/85; one-liner, S. Morris, 3/24/94).

418-040; 037984: "The Acute Oral Toxicity (LD50) and Neurotoxic Effects of Cypermethrin to the Domestic Hen", CTL/C/1077; N.L. Roberts, C. Fairley, D.E. Prentice and L. Cooke; Huntingdon Research Centre, Huntingdon, England; 7/3/81. Technical cypermethrin (batch no P25, 87.8% state purity, nominal cis:trans ratio of 53:47) was given by oral gavage to groups of 10 hens at 0, 2500, 5000, or 10000 mg/kg and observed for 21 days. The hens were then sacrificed and histopathological examinations were done on spinal cord and sciatic nerve. There were no treatment-related effects on body weight, food consumption, ataxia, or histopathology (NOEL and NOAEL > 10000 mg/kg). No adverse effect was indicated. The study was unacceptable and not upgradeable because there were no analytical data for the test material and the dosing solutions, no randomization of the hens, inadequate rationale for the doses, sections of medulla oblongata were not taken, and there was no second dose and 21-day observation period (S. Morris and J. Gee, 11/1/94).

MISCELLANEOUS DOCUMENTS

51970 - 002 173600 Residues of zeta-cypermethrin on alfalfa.

51970 - 076 184006 Residues of zeta-cypermethrin on spinach.

51970 - 077 184007 "Cumulative dietary exposure and risk assessment: zetacypermethrin and cypermethrin." (Watters, J. L., Novigen Sciences, Inc., 6/26/01) The conclusion was that there was reasonable certainty of no harm from use on food crops.

51970 - 078 184008 "Zetacypermethrin and cypermethrin cumulative exposure and risk assessment." (Walls, C. L., Novigen Sciences, Inc., 7/30/01) The conclusion was that there was reasonable certainty of no harm from cumulative exposures.

51970 - 079

US EPA memorandum of September 16, 1983, addressed to T. A. Gardner, regarding a tolerance for cypermethrin on cotton. The document discusses a number of toxicology studies and US EPA interpretations.

Reference 5 contains EPA (3/19/84) and ICI 910/16/85) documents regarding the selection of the NOEL from the 1-year dog study using capsules and whether the NOEL should be 1 mg/kg/day.

51970 - 080 184010 Residue of zeta-cypermethrin on field corn.

51970 - 081 184011 Residue of zeta-cypermethrin on sweet corn.

These documents have been reviewed:

418-022; 001840	418-070; 069574
418-022; 001841	418-098; 091345
418-022; 001842	418-157; 124247
418-017; 003024	418-001; 984934
418-016; 005809	418-005; 984934
418-001; 035022	418-011; 984937
418-001; 035023	418-011; 984938
418-001; 035024	418-012; 984939
418-022; 035025	418-013; 984940
418-040; 037982	418-013; 984941
418-040; 037983	418-166; 133309
418-040; 037984	418-165; 133011
418-040; 037985	418-186; 142302
418-040; 037986	418-186; 142303
418-041; 037987	418-190; 143500
418-042; 037988	418-191; 146312
418-043; 037989	418-193; 146314
418-044; 037990	418-194; 146315
418-045; 037991	418-195; 146316
418-046; 037992	418-197; 146318
418-058; 064620	

These documents are on the Data Index printout but are not found in the volume:

418-057; 062707

These documents are on the Data Index printout but do not contain data about Cypermethrin:

418-058; 064621
418-074; 067058
418-074; 067059
418-115; 118644
418-134; 118780
418-135; 118781
418-136; 118782
418-137; 118783